

## LETTERS TO THE EDITOR

### Vasomotor Effects and Pathophysiologic Relevance of F<sub>2</sub>-Isoprostane Formation in Vascular Diseases

We read with the utmost interest the study by Iuliano et al. (1). The investigators showed for the first time that concentrations of 2-F<sub>2</sub>-isoprostane regioisomers, iPF<sub>2α</sub>-III (15-F<sub>2t</sub>-IsoP) and iPF<sub>2α</sub>-VI (5-F<sub>2t</sub>-IsoP), were markedly increased in the coronary sinus following percutaneous transluminal coronary angioplasty (PTCA). In their study, the levels of iPF<sub>2α</sub>-III in the coronary sinus after angioplasty, measured by GC/NICI-MS, were 125 pg/ml, which is equivalent to 0.35 nmol/l. Such levels are in the same range as plasma samples in nonsmokers (0.103 nmol/l [2], in ruptured aortic aneurysm 0.436 nmol/l [3]) and umbilical cord arterial samples in newborns (0.898 nmol/l [4]), although caution should be taken when comparing these results as the methodology used to measure iPF<sub>2α</sub>-III was different. Such data do not support the conclusion that these concentrations are similar to the EC<sub>50</sub> values observed with iPF<sub>2α</sub>-III on porcine and bovine coronary arteries that are in the micromolar range (5). Indeed, the potency of iPF<sub>2α</sub>-III was in the micromolar range in most studies performed on conductance vessels, including coronary arteries (6), although data on human coronary arteries are lacking.

Consequently, the concentrations observed in this study (1) are unlikely to induce a vasoactive effect in conductance vessels. In contrast, the potency of iPF<sub>2α</sub>-III in the microcirculation is higher, and in some studies close to the nanomolar range (6). As a consequence, whereas the concentrations reported in the Iuliano et al. study (1) are unlikely to contribute to epicardial coronary artery vasoconstriction, local concentrations may be sufficiently high to induce intramyocardial artery vasoconstriction. Further in vivo and in vitro studies are required to determine whether isoprostanes might contribute to vasoconstriction in vascular diseases.

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## REFERENCES

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## REPLY

Cracowski et al. raise an important issue related to the putative biologic effect of F<sub>2</sub>-isoprostanes (iPs) in human coronary arteries after percutaneous transluminal coronary angioplasty (PTCA). We observed an increase of isoprostanes iPF<sub>2α</sub>-III and iPF<sub>2α</sub>-VI in the coronary sinus immediately after PTCA and suggested that this elevation not only reflected reperfusion-mediated oxidative stress but could also play a role in the untoward effects of this procedure. In particular, iPs may facilitate platelet activation and coronary vasospasm, two phenomena that occur early after PTCA and are responsible for coronary thrombosis and arrhythmia.

Used as markers of oxidant stress, F<sub>2</sub>-iPs are increased not only in clinical settings associated with ischemia-reperfusion but also in settings characterized by chronic inflammation such as atherosclerosis, chronic bronchitis and systemic lupus erythematosus (1–3). The F<sub>2</sub>-iPs may also have biologic relevance because they enhance platelet response to the common agonists and elicit a vasomotor response. However, it is still unclear whether these effects can occur in clinical settings associated with enhanced oxidative stress. An in vitro study demonstrated that iPF<sub>2α</sub>-III was not able to elicit platelet aggregation, but in a range of concentration between 10 nmol/l and 10 μmol/l increased the magnitude of platelet response to subthreshold concentrations of arachidonic acid, collagen and adenosine diphosphate (ADP) (4). Patients with diabetes and hypercholesterolemia show a significant correlation between iPF<sub>2α</sub>-III and 1-dehydrothromboxane B<sub>2</sub> values, suggesting a potential link between platelet aggregation and lipid peroxidation (5,6). This was corroborated by the concomitant decrease of iPF<sub>2α</sub>-III and 11-dehydrothromboxane B<sub>2</sub> in patients given 100 to 600 mg/d vitamin E. These data suggest that the circulating levels of iPF<sub>2α</sub>-III may be relevant to clinical settings in which platelet activation and enhanced oxidative stress coexist. Because these two phenomena coincide after PTCA, it is conceivable that a link exists between them, taking into account that in some patients the circulating levels of iPF<sub>2α</sub>-III after PTCA were close to 1 nmol/l. We agree with Cracowski and colleagues that the circulating levels of iPF<sub>2α</sub>-III were likely too low to elicit a direct vasomotor response in the coronary circulation. However, values of the two isoprostane regioisomers measured specifically by us in the coronary sinus cannot be extrapolated to Morrow et al.'s (7) total isoprostane assay with PGF<sub>2α</sub> as internal standard. Even if it did give a quantitative impression of total iPs, this method is quantitatively imprecise, measuring a host of unresolved peaks. Similar amounts of one isoprostane, such as iPF<sub>2α</sub>-III, which is not a very abundant one, suggests that an accurate estimate of total iPs in the coronary circulation would be much higher than in peripheral plasma. Also, it is very difficult to extrapolate from one iP to the effects and local concentration of myriad ones released at the site of free radical burst on the vascular wall.